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ADHD

CAUSES, NEUROCHEMISTRY, AND GENETICS

ADHD: CAUSES, NEUROCHEMISTRY, AND HOW TO CHECK YOUR GENETIC RAW DATA

ADHD (attention deficit hyperactivity disorder) is a condition that usually starts in childhood. It affects around 5% of kids around the world.

Symptoms include inattention, impulsivity, and hyperactivity. Studies show that two-thirds of kids with ADHD will still deal with these issues into adulthood, which can lead to other problems like dropping out of school, getting rejected by peers, injuries, getting in trouble with the law, not doing well in jobs, divorce, and even higher rates of suicide.[ref]

HEREDITY AND ADHD:

Is ADHD hereditary? Twin studies show that the **heritability of ADHD is 70 – 90%** for inattentiveness and hyperactivity.[ref][ref] Heritability is a term that includes genetic variants along with epigenetics and in-utero exposure.

There is no single "ADHD" gene. Instead, researchers have discovered **multiple genetic variants** that contribute in **small ways** to the condition.

Genes related to dopamine, circadian rhythm, neuronal formation, serotonin transporters, tryptophan, and the breakdown of neurotransmitters have all been identified as playing a small role in ADHD. The small changes from multiple variants add up to form the risk for ADHD. It's called a **polygenic risk,** meaning from multiple gene variants.[ref]

RARE MUTATIONS LINKED TO ADHD:

Rare gene mutations have also been investigated to see if they cause ADHD, and it is likely that for a small percentage of people, a rare genetic condition causes it.

ADHD is found at a much higher rate in people with genetic chromosomal abnormalities, including Klinefelter Syndrome (XXY chromosomes), Williams Syndrome (partial deletion in chromosome 7), Turner Syndrome (missing X chromosome), or Fragile X syndrome. [ref]

Additionally, rare mutations in genes identified as ADHD candidate genes are found in higher numbers in people with ADHD.[ref]

In other words: Rare mutations may have a large impact on ADHD for an individual, but it is hard to determine this statistically when looking at a large population group.

JUST A LITTLE MORE DISTRACTED THAN AVERAGE:

Some researchers contend that ADHD is **part of the continuum of normal behavior** — one end of the spectrum. Their conclusion: "The data suggest that ADHD is best viewed as the quantitative extreme of genetic and environmental factors operating dimensionally throughout the distribution of ADHD symptoms, indicating that the same etiologic factors are involved in the full range of symptoms of inattention, hyperactivity and impulsivity." [ref]

HOW IS THE ADHD BRAIN DIFFERENT?

Brain imaging studies show physiological differences in the brains of people with ADHD.

PET scans and SPECT imaging showed that ADHD patients on psychostimulants had increased striatal dopamine transporter density. However, subjects not on stimulant medications had lower dopamine transporter density.[ref]

Another large study found that certain regions of the brain had differences in the cortical surface area in children with ADHD. Specifically, changes were found in the frontal cortex region.[ref] The frontal cortex is responsible for decision-making, reasoning, social appropriateness, and complex cognitive behaviors.

BIOCHEMICAL PATHWAYS INVOLVED IN ADHD:

The latest ADHD genetics research shows that two major pathways are likely involved:

- Dopamine modifications in the striatal neurons
- Altered circadian rhythm

These two pathways are clearly seen in genetic markers related to ADHD (details in the genotype section below).

1) DOPAMINE AND NEUROTRANSMITTERS

The dopamine pathways have been extensively researched in ADHD, which is what methylphenidate (Ritalin) acts on.

The dopamine reuptake transporter (DAT) is found in the striata and is the place where methylphenidate works. Scientists say that more DAT transporters in the striata, caused by genes or the environment, may be the cause of ADHD. However, other results don't agree, showing the inconsistency of ADHD's molecular physiology. [ref]

Dopamine is made from tyrosine utilizing the enzyme tyrosine hydroxylase (TH). Animal studies show that TH is reduced in the striatum of ADHD rats. Treadmill exercise increased TH and decreased ADHD.[ref]

2) CIRCADIAN RHYTHM ALTERATIONS:

While dopamine is integrally related to ADHD symptoms, such as focus and working memory, ADHD patients often also have circadian rhythm abnormalities, including sleep problems.

Circadian rhythm is the 24-hour built-in body clock. In addition to sleep/wake cycles, your circadian rhythm controls the rise and fall of hormones such as cortisol and neurotransmitters such as dopamine. Researchers estimate that about 40% of the body's molecular processes are controlled by the circadian clock.

A recent study looked at gene expression of core circadian clock genes along with the 24-hour profiles of cortisol and melatonin production in people with ADHD. The results showed significant differences in sleep patterns, cortisol rhythm, and the expression of core circadian clock genes (PER2 and BMAL1) in the ADHD group.[ref]

An earlier study found that adults with ADHD had altered BMAL1 and PER2 expression (core circadian rhythm genes).[ref]

Circadian rhythm interacts with dopamine as well. In a cell study using fibroblasts from people with ADHD, researchers found that dopamine significantly altered PER3 levels (core circadian clock gene). This change was not found in cell samples from people without ADHD.[ref] Additionally, the circadian clock regulates the production of enzymes that break down neurotransmitters, such as MAOA.[ref]

Related article: MAOA and the Warrior Gene

ENVIRONMENTAL FACTORS IN ADHD

ADHD is not explained solely by genetics. When it comes to the neurocognitive changes in the ADHD brain, environmental factors that combine with genetic susceptibility are most likely at work.

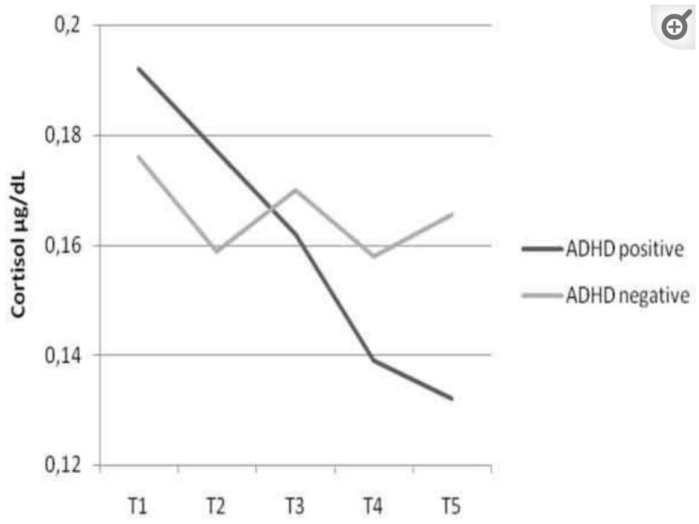
CORTISOL AND INFLAMMATORY MARKERS:

The idea that neural inflammation is at the root of ADHD has been examined in many ways. Conflicting results have been shown on inflammatory biomarkers, with some studies showing slightly increased inflammation and others showing decreased inflammatory markers in children and adults with ADHD.

A review of 19 studies showed that, on average, cortisol levels are lower in youths with ADHD than is typical. Cortisol rises and falls over the course of a day, and the research showed that cortisol levels were lower throughout the day, as well as in cumulative levels.

Additionally, inflammatory markers such as TNF-alpha and IL-1B were also statistically a little lower in kids with ADHD when looking at the combined study data.[ref]

Cortisol response in kids with ADHD is different, though, than in kids without ADHD. A study looked at the response to parental expressed emotions on the kids. The expressed parental emotions caused a greater rise and then fall in cortisol in the kids with ADHD than in kids without ADHD.[ref]



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917389/

While most study results don't show that elevated inflammatory cytokines are a hallmark of ADHD, neuroinflammation may still be a possible cause of ADHD symptoms for individuals. Targeting neuroinflammation may be more important for kids with ADHD who also have altered pain perception and pain sensitivity.[ref]

EXPOSURES TO TOXICANTS BEFORE BIRTH:

Some researchers theorize that environmental disruptions in the fetal environment can impact the developing nervous system, increasing the risk of ADHD and other neurodevelopmental disorders.

Maternal Smoking:
A review of multiple studies found that **maternal smoking** increased ADHD. There was also a link between getting a **serious bacterial or viral infection** (e.g., requiring

hospitalization) while pregnant and an increased risk of the child developing ADHD.[ref] [ref][ref][ref]

Perfluorooctanoic Acid (PFOAs):
PFOAs are man-made persistent chemicals used as stain repellants and food wrapping (to repel oil). Prenatal exposure to PFOA at a higher level was linked to a 3-fold increase in the relative risk of ADHD in children.[ref]

EXPOSURES IN CHILDHOOD:

Phthalates:
Exposure to higher levels of phthalates has been linked to increased ADHD susceptibility in several studies.[ref] Phthalates are common chemicals found in artificial fragrances, adhesives, vinyls, lotions, nail polish, food packaging, and even in boxed mac and cheese. [ref][ref]

Insecticide:
Pyrethroid exposure in children is linked to ADHD. **Pyrethroids** are a class of chemicals used as a pesticide, mostly as a home insecticide as well as for mosquito control. The study found that higher urinary pyrethroid metabolite levels corresponded to increased ADHD, especially impulsivity in boys.[ref]

Lead:
Exposure to lead during early childhood is also linked in many studies to an increased risk of ADHD. While not all studies show this link, the majority of studies in a meta-analysis did show a link between lead exposure, even at low levels, and ADHD.[ref]

Nutrient deficiencies: Can a supplement help ADHD

It would be nice if research showed that a kid with ADHD just needed more of a vitamin or mineral... And a lot of time and money has gone into figuring out whether there is simply a missing element.

Over the past couple of decades, research has shown contradictory results for many different vitamins and minerals. Magnesium, for example, was shown to be a little lower, on average, in kids with ADHD than in kids without ADHD. However, clinical trials on

supplemental magnesium don't show that it has much of an effect — except in kids who are truly deficient.

The evidence seems a little stronger that children with ADHD are likely to have lower zinc and iron levels than the control group without ADHD. Again, supplementation studies don't show that restoring mineral levels effectively mitigates symptoms.[ref][ref][ref]

I want to point out, though, that what holds true for a group of kids with ADHD may not be true for an individual. It is possible that magnesium, zinc, or iron could be key for an individual who is deficient in that mineral.

WHAT HAPPENS WHEN ADHD KIDS GROW UP?

Studies show that 60-70% of kids with ADHD still have problems with symptoms as adults. While some kids may 'grow out of it', around two-thirds will still deal with ADHD as an adult. This speaks to the need for lifestyle adaptations and natural options for managing ADHD as an adult.

But what happens as you head toward old age? In general, brain volume decreases with aging. However, studies show there is less brain shrinkage in people over 60 who have been diagnosed previously with ADHD. It is hard to know, though, whether ADHD itself is neuroprotective or if the medications for ADHD are having an effect on brain volume.[ref]

PROBLEMS THAT GO ALONG WITH ADHD:

Whether due to overlapping genetic susceptibility or other factors, research shows that people with ADHD are at an increased risk of other mental health disorders:[ref]

- Increased risk of substance misuse disorders
- 9-fold increased risk of problematic media use (teens)
- Eating disorders are increased in ADHD
- Increased risk of migraines
- 2 to 3-fold increased risk of epilepsy

HIGH HISTAMINE AND ADHD:

A large meta-analysis looked at the overlap between atopic disease and ADHD. Atopic diseases include atopic dermatitis (eczema), allergic rhinitis, and asthma. The analysis included data from 38 studies with over 100,000,000 participants. The results showed that atopic diseases were increased in kids with ADHD compared to kids without ADHD. [ref]

Why is this important – the overlap of eczema, sinus allergies, and asthma with ADHD? It could mean that the underlying pathways involved in ADHD are also involved in atopic diseases. Atopic diseases are connected to inflammation and Th1, Th2, and Th17 immune responses. This ties into excess IgE and histamine production.

Histamine acts as a neurotransmitter in the brain. Histamine levels rise in the morning hours, making us feel alert when we wake up. (diphenhydramine makes you sleepy because it blocks the histamine receptors in the brain...).

Animal studies show that the HNMT (histamine n-methyltransferase) enzyme is essential for breaking down histamine in the brain. Brain histamine acts on various functions, including appetite, stress response, sleep-wake cycles, and memory.[ref]

Interestingly, one of the genetic variants related to higher histamine levels in the brain (the HNMT gene) is linked to ADHD susceptibility.[ref] Another study showed that kids with a specific HNMT variant were sensitive to food coloring additives, including red and yellow dyes, relating ADHD to food additive reactions.[ref]

THAT WHICH SHOULD NOT BE SPOKEN OF...

I'm going to touch on the research on two more controversial aspects of ADHD research. Please click through to the referenced studies for more in-depth information.

VACCINATIONS:

A study involving over 4,000 kids examined the question of whether exposure to thimerosal-containing vaccinations (hepatitis B) increased the risk of ADHD. After

adjusting for a bunch of variables (demographics, socioeconomics, health issues), researchers found that kids who were vaccinated with the **thimerosal**-containing hepatitis B vaccine had almost **twice the risk of ADHD**. The thimerosal-containing hep B vaccine was given between 1991 and 2001 to infants in the US.[ref]

Thimerosal is a mercury-based preservative widely used for decades in vaccines. However, starting in the early 2000s, thimerosal was removed from almost all childhood vaccines (the exception being the flu vaccine). The FDA states that thimerosal is safe in vaccines.[ref]

A study of Tdap-vaccination in pregnant women shows no statistical difference in ADHD rates of their children.[ref]

ACETAMINOPHEN USAGE IN PREGNANCY:

Another interesting connection to rising ADHD levels may be prenatal exposure to acetaminophen. Essentially, acetaminophen is broken down through glucuronidation, sulfation, and the CYP2E1 enzyme – and these routes of detoxification don't work the same in utero or even in premature babies.[ref]

Acetaminophen crosses the placental barrier and remains in an infant's blood circulation for a longer duration. Animal studies show that unmetabolized acetaminophen may inhibit certain routes of brain development as well as fetal testosterone production.[ref]

Epidemiological studies show that there is an association between maternal acetaminophen use and ADHD rate. A study using cord blood metabolites as well as maternal acetaminophen use found that a higher acetaminophen burden was associated with a **2 to 3-fold** increase in the risk of ADHD.[ref]

IS ADHD ON THE RISE SIMPLY BECAUSE IT IS OVERDIAGNOSED?

One question that frequently comes to mind for me is whether a condition that seems to be on the rise is being overdiagnosed – perhaps due to the availability and promotion of pharmaceuticals for the condition.

A scoping review of 334 research studies on ADHD concluded that overdiagnosis is common in children and adolescents. Broadening of the diagnostic criteria may be one

reason for this. The researchers caution that long-term harm could be associated with diagnosing and treating ADHD in children with milder symptoms.[ref]

Studies with school-aged kids show that younger children in a class (late birthdays) are more likely to be diagnosed and medicated for ADHD compared to kids whose birthdays fall earlier in the school year.[ref] This raises the question of whether the younger kids are just not developmentally ready for the sit-down learning environment.

Does overdiagnosis account for the entire rise in ADHD cases? The same review of 334 studies found that ADHD diagnoses have steadily increased since 1989, and overdiagnosis was most likely not the sole cause.[ref]

The genotype report section is found in the full article: https://www.geneticlifehacks.com/adhd-genes/

LIFEHACKS: NATURAL SOLUTIONS FOR ADHD

There are a ton of studies on ADHD that involve lifestyle changes, diet, circadian rhythm, or natural supplements. Please click through to the references for details on each of the studies. Talk with your doctor if you have questions or need medical advice.

DIET:

Does diet affect ADHD? An unhealthy diet can exacerbate symptoms.

Studies show that kids with ADHD are generally more likely to eat a less healthy diet.[ref] Overall, a healthy diet, higher in whole foods, should be a **baseline** to strive for when it comes to optimal cognitive health – for adults and children.

Studies also show that **maternal diet** is linked to ADHD in children. Mothers with particularly poor diets were more likely to have kids with ADHD.[ref]

Low histamine diet:
A low histamine diet may help with symptoms. Additionally, eliminating yellow and red food coloring may be worth a shot.

- **Who Likely Benefits:** Individuals with HNMT gene variants (rs1050891 A/A)
- Actions:
    - Avoid high-histamine foods (e.g., aged cheeses, fermented products, processed meats, tomato sauce, spinach, chocolate, strawberries, etc.)
    - Eliminate yellow and red food coloring

Related article: Histamine intolerance and a low-histamine diet.

Few-foods diet:
A study using the 'few-foods diet' found that it decreased ADHD symptoms in 60% of kids. A 'few foods diet' restricts eating to foods with lower allergenic potential. An example of the few-foods diet would include turkey, lamb, cruciferous vegetables, carrots, peas, white potatoes, rice, apples, and pears.[ref]

- **Who Likely Benefits**: Children with food sensitivities
- **Actions:**
    - Limit diet to low-allergenic foods (e.g., turkey, lamb, specific vegetables and fruits)
    - Gradually reintroduce foods to identify triggers

CIRCADIAN RHYTHM AND MELATONIN PRODUCTION:

Circadian rhythm disruption is at the heart of ADHD for some people – and likely adds to symptoms for everyone. Just think about how you feel when you are jet lagged or have had an unusually late night.

Bright light exposure early in the day increases melatonin production at night. A trial that included 30 minutes of bright light in the morning and minimizing overhead lights in the evening showed significantly decreased ADHD symptom scores.[ref]

A study in adults with ADHD compared a placebo to 0.5 mg/d of melatonin or 0.5 mg/d melatonin along with bright light exposure for 30 minutes in the morning. Bright light exposure plus melatonin advanced the onset time of melatonin production in the evening by almost two hours. Additionally, ADHD symptoms were reduced by 14% in the melatonin groups (no response in the placebo group). Stopping supplemental melatonin or melatonin plus bright light caused ADHD symptoms to return to baseline in a couple of weeks.[ref]

- **Who May Benefit**: Individuals with CLOCK (rs1801260 A/A), ARNTL2 (rs2306074 C/T), PER1 (rs2518023 G/G) variants
- **Actions:**
  - Bright light exposure in the morning
  - Blocking blue light – or melatonin supplement for older adults – in the evening
  - Consistent sleep schedule
  - Consistent eating schedule

EXERCISE OR SPORTS:

Exercise enhances dopamine release and improves executive function. An overview of studies on exercise in kids with ADHD showed a measurable but moderate benefit following acute exercise on executive function.[ref] Additionally, a 12-week training program for kids found that the general sports skills training improved working memory. [ref]

- **Who May Benefit:** Individuals with SNAP-25 (rs3746544 T/T), SLC6A3 (rs27072 C/C) variants

- **Actions:**
  - Regular aerobic exercise
  - Sports and physical training programs

NATURAL SUPPLEMENTS FOR ADHD:

Please be sure to talk with your doctor if you have any questions about supplements or interactions with medications.

Check COMT First: Before you start on a new supplement, if you have the slow version of the COMT variant, check out the full article on how COMT interacts with methyl donor supplements. In a nutshell, overwhelming the COMT enzyme can cause neurotransmitter levels to fluctuate. This can cause irritability, anxiety, anger, etc. So check this gene to make sure that you aren't exacerbating ADHD symptoms with methyl donors or other supplements that you are taking.

1. Saffron:
Multiple clinical trials show that saffron (20-30 mg/d) is as effective as methylphenidate (Ritalin) for ADHD symptoms in children and adults. Saffron increases the release of dopamine, serotonin, and noradrenaline.[ref]

- **Benefits**: Increases dopamine, serotonin, and norepinephrine
- **Dosage**: 20-30 mg/day
- **Possible Genetic Interactions**: Individuals with HTR1B1 (rs6296 C/G) and other neurotransmitter gene variants

2. Magnesium L-Threonate:
A small trial in adults with ADHD found that half of the participants had an improvement in symptoms with 12 weeks of l-threonic acid magnesium.[ref]

- **Benefits**: Improves cognitive function
- **Possible Genetic Interactions**: Individuals with SNAP-25 (rs3746544 T/T)

3. Vitamin D plus Magnesium:
A placebo-controlled trial in children with ADHD found that 50,000 IU/week of vitamin D

plus magnesium supplements improved emotional, conduct, peer, and social problems. [ref]

A trial of magnesium for kids with ADHD who were also magnesium deficient found a decrease in hyperactivity after six months.[ref]

- **Benefits**: Improves emotional and social problems
- **Dosage**: 50,000 IU/week of vitamin D (under medical supervision), 200 mg/day of magnesium
- **Who May Benefit**: Individuals with vitamin D or magnesium deficiency

4. Bacopa monnieri:
A clinical trial of 225 mg/day in 6-12-year-old ADHD patients showed that bacopa monnieri reduced restlessness scores in 93% of the kids and improved attention-deficit symptoms in 85% of the children.[ref]

- **Benefits**: Reduces restlessness, improves attention
- **Dosage**: 225 mg/day
- **Who May Benefit**: Individuals with DRD4 (rs1800955 C/C) and ANKK1 gene variants

5. Zinc:
A randomized placebo-controlled trial of zinc sulfate supplements found that after 12 weeks, there were greater improvements in hyperactivity and impulsiveness but not in attention deficiency symptoms.[ref]

- **Benefits**: Improves hyperactivity and impulsiveness
- **Doses:** 34 mg/day (high dose, under medical guidance)
- **Dietary sources:** Foods high in zinc include oysters, pumpkin seeds, cashews, and dark chocolate
- **Who May Benefit**: Individuals with dopamine transporter SLC6A3 variants

6. L-theanine plus caffeine:
A clinical trial of 2.5 mg l-theanine and 2 mg/kg of caffeine showed that the combination improved inhibitory cognition and inhibitory control (adults).[ref]

- **Benefits**: Improves inhibitory control
- **Who May Benefit**: Adults with ADHD

7. Lithium orotate:
Some clinicians recommend low-dose lithium orotate for ADHD.[ref] I am not able to find any specific research on low-dose lithium for ADHD in kids, though. In adults with ADHD, a study using high-dose lithium found that it was as effective as methylphenidate in reducing irritability, aggressive outbursts, and more.[ref] In animals, lithium increases working memory.[ref] Low-dose lithium is also being used in Alzheimer's disease.[ref]

- **Benefits**: Reduces irritability, aggression
- **Who May Benefit**: Adults, read about genetic interactions between lithium orotate and B12

8. Omega-3s, zinc, plus magnesium:
A 12-week trial that included 810 children found that the combination of EPA, DHA, zinc, and magnesium "showed a considerable reduction in symptoms of attention deficit and hyperactivity/impulsivity assessed by SNAP-IV".[ref]

- **Benefits**: Reduces hyperactivity and impulsivity
- **Doses:** 400 mg omega-3s, 5mg zinc, 80mg magnesium – children aged 5-12 in the study
- **Who May Benefit**: Anyone not regularly eating foods, such as fish, that are high in DHA, EPA, and zinc

9. N-acetylcysteine (NAC):
A clinical trial showed that NAC (2.5mg/day) reduced ADHD symptoms in patients who also had an autoimmune disease.[ref]

ENVIRONMENTAL TOXINS LINKED TO ADHD:

Phthalates:
Research shows that high phthalate levels are linked to increased ADHD risk. [ref]

- **Avoid**: Phthalates in artificial fragrances, adhesives, vinyls, lotions, nail polish, food packaging, and even in boxed mac and cheese.[ref][ref]

Insecticide:
Pyrethroid exposure in children is linked to ADHD.[ref]

- **Avoid:** home pesticides that include pyrethroid, mosquito sprays that include pyrethroid

Lead:
Exposure to lead during early childhood is also linked in many studies to an increased risk of ADHD. [ref]

- **Avoid:** Check your water for lead. Avoid lead-based paints on toys.

The full and up-to-date version of this article is found at:
https://www.geneticlifehacks.com/adhd-genes/